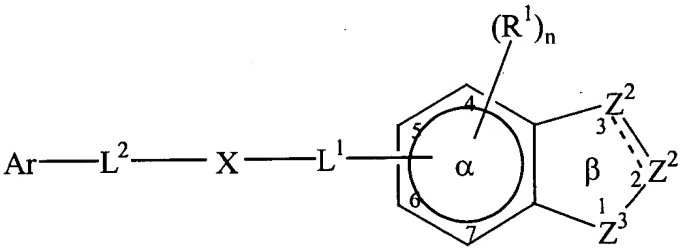
Abstract

The invention is directed to inhibition of p38-α kinase using compounds of the formula



(1)

and the pharmaceutically acceptable salts thereof, or a pharmaceutical composition thereof, wherein

Ar is an aryl group substituted with 0-5 non-interfering substituents, wherein two adjacent noninterfering substituents can form a fused aromatic or nonaromatic ring;

L^1 and L^2 are linkers;

X is an aliphatic monocyclic or aliphatic polycyclic moiety optionally comprising one or more hetero ring atoms wherein the cyclic moiety may be optionally substituted with one or more noninterfering substituents and where said optional substituents may constitute a ring fused to X;

n is 0-3;

each R^1 is hydrogen or a noninterfering substituent;

 represents a single or double bond;

one Z^2 is CA or CR^2A; the other Z^2 is CR^3, CR^3_2, NR^4 or N; and each R^2, R^3 and R^4 is independently hydrogen or a noninterfering substituent;

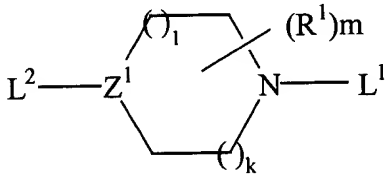
Z^3 is NR^5 or O; where R^5 is hydrogen or a noninterfering substituent;

A is $-W_i-COX_jY$, where Y is COR^6 or an isostere thereof, each of W and X is a spacer of 2-6Å; each of i and j is independently 0 or 1; and R^6 is a noninterfering substituent;

and wherein the smallest number of covalent bonds in the compound separating the atom of Ar linked to L^2 and the atom of the α ring linked to L^1 is at least 5, each said

bond having a bond length of 1.2 to 2.0 angstroms; and/or the distance in space between the atom of Ar linked to L^2 and the atom of the α ring linked to L^1 is 4.5 –24 angstroms;

and with the proviso that the portion of the compound represented by L^2-X-L^1 is not:



where L^2 and L^1 are linkers; Z^1 is CR or N wherein R is hydrogen or a non-interfering substituent; each R^1 is independently a non-interfering substituent; and each of l and k is 0-3; and m is 0-4.